REMARKS

The Specification has been amended to update the reference to prior application 08/670,006, in order to indicate that it is now US Patent 6,150,500. The Specification has also been amended to include SEQ ID references as requested by the Examiner. No new matter has been added.

Objection to Claims 31, 33, 48 and 50

The Examiner objected to Claims 31, 33, 48 and 50, as well as to the Specification, stating that the claims and the Specification needed to be in conformity with the Sequence Rules and Regulations. Claims 31 and 48 have been amended to specify that amino acids 590-650 of endothelial nitric oxide synthase are SEQ ID NO:30, aa 78-138; and Claim 33 and 50 have been amended to specify that amino acids 820-880 of neuronal nitric oxide synthase are SEQ ID NO:31, aa 83-143. The Specification has also been appropriately corrected. No new matter has been added.

Rejection of Claims 31, 33, 48 and 50 under 35 U.S.C. 112, second paragraph

The Examiner rejected Claims 31, 33, 48 and 50, stating that the phrases, "amino acids 590-650 of endothelial nitric oxide synthase" and "amino acids 820-880 of neuronal nitric oxide synthase" were vague and indefinite. The Claims have been amended to incorporate sequence identifiers, in order to more distinctly point out and claim the invention.

Rejection of Claims 32, 48, 49 and 50 under 35 U.S.C. 112, first paragraph

The Examiner rejected Claims 32 and 49, stating that one of ordinary skill in the art, given the teachings of the Specification, would not expect SEQ ID NO: 4 or 5 (the negatively charged loop of INOS), or 8 or 9 (sequences of nNOS) to interact with the regulatory region of eNOS.

In order to facilitate prosecution of the application, the claims have been amended to specify that the constitutive nitric oxide synthase activator peptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8,

and SEQ ID NO. 9. These are the sequences related to eNOS and nNOS (see, e.g., the Specification at p. 15, lines 17-19).

As described in the Specification, eNOS and nNOS are structurally very closely related. Both eNOS and nNOS are constitutive enzymes, which are controlled by intracellular calcium and the regulatory protein calmodulin (CAM) (see, e.g., p. 25, lines 19-29). Both of these constitutive NOS enzymes have extensive insertions within the FMN binding domain, about 100 residues downstream from the calmodulin binding site; the insert is spatially adjacent to the calmodulin binding site (see, e.g., p. 27, lines 10-19). Interaction between calmodulin and the insert turns the constitutive NOS enzyme on; thus, ligands which interact with the insert and the adjacent region of the FMN domain will force the switching mechanism into the off state or the on state (see, e.g., p. 27, lines 22-26).

The negatively charged loops of eNOS (SEQ ID NO: 6 and 7, which are amino acids 557-570 and 666-680, respectively) are adjacent to the regulatory region of eNOS (amino acids 590-650). Similarly, the negatively charged loops of nNOS (SEQ ID NO: 8 and 9, which are amino acids 790-803 and 897-911, respectively) are adjacent to the regulatory region of nNOS (amino acids 820-880). One of ordinary skill in the art, given the teachings of the Specification regarding the close relationship between the structure of the two constitutive NOS enzymes, as well as the similar method of activation of the two enzymes, would reasonably expect that amino acid sequences comprising the negatively charged loops of nNOS would have a similar effect both on the regulatory region of nNOS and also on the regulatory region of eNOS.

The Examiner also rejected Claims 48, 49 and 50, stating that the claims drawn to a "disease modulated by nitric oxide" read on diseases caused by overproduction as well as by underproduction of nitric oxide. Applicant does not concur; however, in order to expedite prosecution of the application, the claims have been amended to specify that the disease is treated by increasing the production of nitric oxide by endothelial nitric oxide synthase in a mammal.

CONCLUSION

In view the amendments and discussion presented above, the application is in condition for allowance. Applicant's Attorney respectfully requests the Examiner to reconsider and withdraw all rejections.

If the Examiner believes that a telephone conversation would expedite prosecution of the application, the Examiner is invited to call Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to call David E. Brook at (978) 341-0036.

Respectfully submitted,

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